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ORIGINAL ARTICLE

Ultrasound mediated synthesis of 6-substituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinoline derivatives and their pharmacological evaluation

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KEYWORDS

Pyrrolo[3,2,1-*ij*]quinoline;
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Cytotoxicity

Abstract Designed as potential cytotoxic agents a series of 6-substituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinoline derivatives were synthesized by using a Bischler type reaction. The methodology involved the cyclodehydration of 2-(3,4-dihydroquinolin-1(2*H*)-yl)-1-alkyl/aryl ethanones in the presence of *p*-TSA under ultrasound irradiation. A number of compounds were prepared using this methodology and tested for their *in vitro* anti-proliferative properties against cancer (leukemia) and non-cancerous cell lines. Some of the compounds showed promising and selective cytotoxic effects toward leukemia cells.

1. Introduction

The pyrrolo[3,2,1-*ij*]quinoline framework has been found to be an integral part of several bioactive molecules and agents (Stanton and Ackerman, 1983; Al-awar et al., 2004). For example, compounds containing this framework were found to be useful for the potential treatment of asthma (Paris et al., 1995), epilepsy, obesity (Isaac et al., 2000) and rice blast diseases (Bass et al., 1981). This framework attracted our attention because of a recent report that disclosed anti-leukemic activity of a series of polycyclic isatin derivatives including pyrrolo[3,2,1-*ij*]quinoline-1,2-diones (Matesic et al., 2012). Indeed, the compound **A** (Fig. 1) that belongs to this class showed notable cytotoxicity (IC_{50} = 8.36 ± 3.5 μM) when tested against U937 cells. This report and our interest (Layek et al., 2009a,b, 2011; Rao et al., 2014) in this class of compounds prompted us to evaluate a library of compounds based on 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinoline framework **B** (Fig. 1). The substituent "R" was introduced at C-6 position of the tricyclic ring not only for the creation of diversity but

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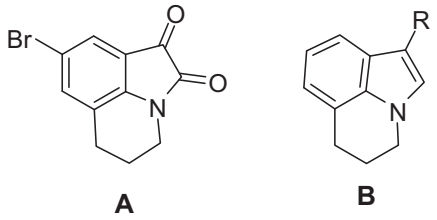


Figure 1 The known pyrrolo[3,2,1-*ij*]quinoline-1,2-dione derivative **A** and the new framework **B** for the identification of potential cytotoxic agents.

also for the fact that 3-substituted indoles were found to be antiproliferative agents (Rao et al., 2011).

While a number of methods have been reported for the construction of pyrrolo[3,2,1-*ij*]quinoline or related rings all of them involved in the use of expensive transition metals especially Pd/Cu catalysts (Layek et al., 2009a,b, 2011; Rao et al., 2014; Marchand et al., 2005; Blurton et al., 1997; Dorow et al., 2006). Moreover, all these methods are useful for accessing compounds having a substituent at C-5 position and not handy for the synthesis of compounds based on **B**. A literature search revealed that the Bischler (Bischler and Brion, 1892; Bischler and Fireman, 1893) type of reaction (Shikhaliev et al., 2003; Wijngaarden et al., 1993; Zhu et al., 2004; Adam-Worrall, 2005) has been explored to prepare tricyclic compounds possessing a substituent at C-6 similar to **B**. For example, *N*-phenacyl derivatives of hydroquinolines were cyclized to the corresponding pyrroloquinolines in the presence of an acid catalyst (Shikhaliev et al., 2003). We therefore decided to adopt a similar but faster strategy for accessing our target compounds based on **B**. The ultrasound mediated reactions have gained considerable interest in recent time. Compared to the traditional methods the ultrasound mediated reactions offer several advantages such as shorter reaction time, mild conditions, and good yields of products (Li et al., 2005; Ratoarinoro et al., 1992). Thus, the use of ultrasound radiation has emerged as a common strategy in present day organic synthesis. Herein we report an ultrasound mediated faster approach toward 6-substituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinoline derivatives (**3**) *via* a Bischler type reaction of 2-(3,4-dihydroquinolin-1(2*H*)-yl)-1-alkyl/aryl ethanone (**2**) prepared from 1,2,3,4-tetrahydroquinoline (**1**) (Scheme 1). To our knowledge the present strategy has not been explored for the preparation of compound **3** earlier. We also report the cytotoxicity of the synthesized compounds tested against human chronic myeloid leukemia cells i.e. K562 *in vitro*. Being a cancer of the blood-forming tissues, leukemia is characterized by a large increase in the numbers of white blood cells (leukocytes) in the circulation or bone marrow.

2. Material and methods

2.1. General methods

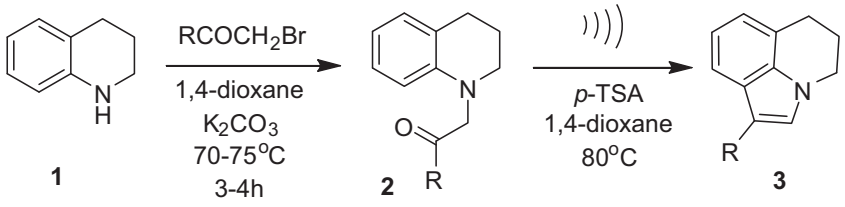
Unless stated otherwise, reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F_{254}), visualizing with ultraviolet light or iodine spray. Column chromatography was performed on silica gel (60–120 mesh) using distilled petroleum ether and ethyl acetate. ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ solution using a Varian 400 MHz spectrometer. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.0$) as internal standard and expressed in parts per million. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. Infrared spectra were recorded on a FTIR spectrometer. Melting points were determined by using a Buchi melting point B-540 apparatus. MS spectra were obtained on a mass spectrometer.

2.2. Preparation of compound *2*

To a solution of compound **1** (1 mmol) and α-bromo ketone (0.95 mmol) in 1,4-dioxane (5 mL) was added K_2CO_3 (1 mmol) and the mixture was stirred at 70–75 °C for 3–4 h under nitrogen. After completion of the reaction (indicated by TLC) the mixture was concentrated under reduced pressure and diluted with cold water (25 mL). The mixture was extracted with EtOAc (3 × 5 mL). The combined organic layer was collected, washed with water (2 × 5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under low vacuum. The product obtained was used for the next step.

2.3. General procedure for the preparation of compound *3*

A solution of compound **2** (1 mmol) and *p*-TSA (0.5 mmol) in 1,4-dioxane (3 mL) was heated at 80 °C in the presence of nitrogen under ultrasound (using a laboratory ultrasonic bath SONOREX SUPER RK 510H model producing irradiation of 35 kHz) for 2 h. The reaction mixture was then concentrated under vacuum, diluted with EtOAc (10 mL), and washed with 1 N K_2CO_3 solution (2 × 5 mL) followed by cold water. The EtOAc layer was collected, dried over anhydrous Na_2SO_4, filtered and concentrated under low vacuum. The crude product isolated was purified by column chromatography over silica gel using hexane–EtOAc as eluant.



Scheme 1 Ultrasound mediated synthesis of 6-substituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinoline derivatives (**3**) *via* a Bischler type reaction.

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2.4. 1-Phenyl-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline ***(3a)***

Light yellow solid; mp 61–63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.9 Hz, 1H), 7.68–7.66 (m, 2H), 7.42–7.39 (m, 2H), 7.26–7.21 (m, 2H), 7.10–7.07 (m, 1H), 6.95 (d, J = 7.0 Hz, 1H), 4.17 (t, J = 6.0 Hz, 2H), 3.02 (t, J = 6.0 Hz, 2H), 2.27–2.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 135.0, 128.7, 126.8, 125.4, 123.7, 123.6, 122.0, 120.3, 119.0, 117.5, 116.5, 44.1, 24.7, 22.6; MS (ESI) m/z: 233 (100), 232 (33), 204 (6), 154 (5), 88 (2); HRMS (ESI) for $C_{17}H_{16}N$ (M + H)+: calcd 234.1277, found 234.1285.

2.5. 1-(4-Fluorophenyl)-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline ***(3b)***

Oily liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.3 Hz, 2H), 7.20 (s, 1H), 7.14–7.04 (m, 3H), 6.95 (d, J = 7.0 Hz, 1H), 4.18 (t, J = 6.0 Hz, 2H), 3.02 (t, J = 6.0 Hz, 2H), 2.30–2.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1 (d, J C – F = 242.5 Hz), 134.8, 132.1 (d, J C – F = 3.1 Hz), 128.1 (d, J C – F = 7.6 Hz), 123.6, 123.4, 122.0, 120.4, 119.0, 117.1, 115.6, 115.5 (d, J C – F = 21.1 Hz), 44.1, 24.6, 22.7; MS (ESI) m/z: 251 (100), 232 (9), 207 (5), 154 (11), 125 (11) 75 (4); HRMS (ESI) for $C_{17}H_{15}FN$ (M + H)+: calcd 252.1183, found 252.1180.

2.6. 1-(4-Chlorophenyl)-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline ***(3c)***

Light brown solid; mp 125–127 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.0 Hz, 1H), 7.59–7.56 (m, 2H), 7.37–7.34 (m, 2H), 7.23 (s, 1H), 7.09 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 7.0 Hz, 1H), 4.16 (t, J = 6.0 Hz, 2H), 3.00 (t, J = 6.0 Hz, 2H), 2.26–2.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0, 134.6, 131.0, 128.8, 128.0, 123.7, 123.5, 122.1, 120.5, 119.1, 117.2, 115.3, 44.2, 24.6, 22.7; MS (ESI) m/z: 267 (100), 266 (36), 230 (15), 154 (11), 88 (25) 75 (10); HRMS (ESI) for $C_{17}H_{15}ClN$ (M + H)+: calcd 268.0888, found 268.0884.

2.7. 1-(4-Bromophenyl)-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline ***(3d)***

Pale yellow solid; mp 153–155 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.68 (m, 1H), 7.56–7.52 (m, 4H), 7.27 (s, 1H), 7.12 (d, J = 7.9 Hz, 1H), 6.98 (d, J = 7.0 Hz, 1H), 4.20 (t, J = 6.0 Hz, 2H), 3.02 (t, J = 6.0 Hz, 2H), 2.30–2.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.1, 135.0, 131.7, 128.2, 123.8, 123.4, 122.1, 120.6, 119.1, 118.8, 117.2, 115.3, 44.2, 24.6, 22.7; MS (ESI) m/z: 311 (100), 313 (98), 312 (40), 230 (20), 102 (15); HRMS (ESI) for $C_{17}H_{15}BrN$ (M + H)+: calcd 312.0382, found 312.0376.

2.8. 1-(p-Tolyl)-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline ***(3e)***

Ash colored solid; mp 101–103 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.1 Hz, 1H), 7.57 (d, J = 7.4 Hz, 2H), 7.24–7.22 (m, 3H), 7.07 (t, J = 7.4 Hz, 1H), 6.94 (d, J = 7.0 Hz, 1H), 4.18 (t, J = 6.0 Hz, 2H), 3.01 (t, J = 6.0 Hz, 2H), 2.38 (s, 3H), 2.28–2.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.0, 133.8, 132.1, 128.5, 125.7, 122.6, 122.3, 120.8, 119.1, 117.7, 116.4, 115.5, 43.0, 23.6, 21.7, 20.0; MS (ESI) m/z: 247 (100), 246 (35), 231 (8), 154 (10), 128 (16) 73 (4); HRMS (ESI) for $C_{18}H_{18}N$ (M + H)+: calcd 248.1434, found 248.1431.

2.9. 1-(4-Methoxyphenyl)-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline ***(3f)***

Pale yellow solid; mp 124–126 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.1 Hz, 1H), 7.62–7.60 (m, 2H), 7.20 (s, 1H), 7.07 (d, J = 8.0 Hz, 1H), 7.01–6.95 (m, 3H), 4.18 (t, J = 6.0 Hz, 2H), 3.86 (s, 3H), 3.00 (t, J = 6.0 Hz, 2H), 2.29–2.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 134.8, 128.7, 128.1, 123.7, 123.2, 122.0, 120.1, 118.9, 117.6, 116.4, 114.3, 55.3, 44.3, 24.9, 22.9; MS (ESI) m/z: 263 (100), 248 (92), 240 (11), 192 (60), 131 (12); HRMS (ESI) for $C_{18}H_{18}NO$ (M + H)+: calcd 264.1383, found 264.1380.

2.10. 4-(5,6-Dihydro-4H-pyrrolo[3,2,1-ij]quinolin-1-yl)benzonitrile ***(3g)***

Ash colored solid; mp 133–135 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.71 (m, 3H), 7.66–7.64 (m, 2H), 7.37 (s, 1H), 7.14 (d, J = 7.9 Hz, 1H), 7.01 (d, J = 7.0 Hz, 1H), 4.20 (t, J = 6.0 Hz, 2H), 3.01 (t, J = 6.0 Hz, 2H), 2.29–2.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 135.2, 132.5, 126.4, 125.0, 123.3, 122.4, 121.2, 119.5, 119.6, 117.2, 114.7, 108.1, 44.4, 24.6, 22.5; MS (ESI) m/z: 258 (100), 242 (5), 230 (6), 202 (4), 128 (8); HRMS (ESI) for $C_{18}H_{15}N_2$ (M + H)+: calcd 259.1230, found 259.1226.

2.11. 1-(Naphthalen-2-yl)-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline ***(3h)***

Light brown solid; mp 113–115 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.89–7.85 (m, 3H), 7.83–7.80 (m, 2H), 7.49–7.45 (m, 1H), 7.43–7.39 (m, 2H), 7.14 (d, J = 7.8 Hz, 1H), 7.01 (d, J = 7.0 Hz, 1H), 4.21 (t, J = 6.0 Hz, 2H), 3.03 (t, J = 6.0 Hz, 2H), 2.32–2.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0, 134.1, 133.5, 131.7, 128.1, 127.6, 127.7, 126.0, 126.1, 125.0, 124.2, 124.1, 123.8, 122.1, 120.5, 119.1, 117.6, 116.4, 44.2, 24.7, 22.6; MS (ESI) m/z: 283 (100), 254 (7), 226 (5), 141 (8), 139 (4); HRMS (ESI) for $C_{21}H_{18}N$ (M + H)+: calcd 284.1434, found 284.1428.

2.12. 1-(3a,7a-Dihydrobenzofuran-2-yl)-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline ***(3i)***

Ash colored solid; mp 136–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.9 Hz, 1H), 7.60 (s, 1H), 7.54–7.53 (m, 1H), 7.47–7.46 (m, 1H), 7.20–7.15 (m, 3H), 7.00 (d, J = 7.0 Hz, 1H), 6.85 (d, J = 0.4 Hz, 1H), 4.19 (t, J = 6.0 Hz, 2H), 3.01 (t, J = 6.0 Hz, 2H), 2.28–2.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 153.4, 134.7, 130.1, 124.6, 122.8, 122.7, 122.5, 122.2, 121.0, 120.0, 119.5, 117.7, 110.4, 107.1, 98.7, 44.4, 24.5, 22.7; MS (ESI) m/z: 273 (100), 245 (6), 189 (3), 136 (6), 120 (3); HRMS (ESI) for $C_{19}H_{18}NO$ (M + H)+: calcd 274.1226, found 274.1221.

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2.13. Ethyl 2-(5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-1-yl) acetate (3j)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.0 Hz, 1H), 7.03–7.00 (m, 2H), 6.89 (d, J = 7.0 Hz, 1H), 4.14 (q, J = 7.0 Hz, 2H), 4.09 (t, J = 6.0 Hz, 2H), 3.73 (s, 2H), 2.94 (t, J = 6.0 Hz, 2H), 2.22–2.17 (m, 2H), 1.26–1.23 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 134.2, 125.1, 125.0, 121.5, 119.4, 118.4, 116.5, 106.7, 60.4, 44.0, 31.5, 24.4, 22.6, 14.1; MS (ESI) m/z: 170 (100), 142 (27), 243 (3), 83 (2); HRMS (ESI) for $C_{15}H_{18}NO_2$ (M + H)+: calcd 244.1332, found 244.1329.

2.14. 1-Ethyl-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline (3k)

Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 7.7 Hz, 1H), 7.00–6.95 (m, 1H), 6.87 (d, J = 7.0 Hz, 1H), 6.83 (s, 1H), 4.11–4.04 (m, 2H), 2.97 (t, J = 5.9 Hz, 2H), 2.78–2.74 (m, 2H), 2.22–2.19 (m, 2H), 1.32–1.29 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4, 125.0, 122.5, 121.4, 118.7, 118.1, 117.2, 116.4, 43.6, 24.5, 23.0, 18.5, 15.0; MS (ESI) m/z: 185 (37), 170 (100), 168 (4), 142 (16), 115 (5); HRMS (ESI) for $C_{13}H_{16}N$ (M + H)+: calcd 186.1277, found 186.1273.

2.15. MTT assay

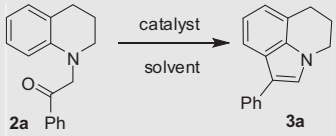
Cell viability was determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cells (5×10^3 cells/well) were seeded to 96-well culture plate and cultured with or without compounds at 10 µM concentration (five different concentrations i.e., 10, 5, 1, 0.5, and 0.1 µM for dose response study) in duplicates for 24 h in a final volume of 200 µl. After treatment, the medium was removed and 20 µl of MTT (5 mg/ml in PBS) was added to the fresh medium. After 3 h incubation at 37 °C, 100 µl of DMSO was added to each well and plates were agitated for 1 min. Absorbance was read at 570 nm on a multi-well plate reader (Victor3, Perkin Emler). Percent inhibition of proliferation was calculated as a fraction of control (without compound).

3. Results and discussion

3.1. Chemistry

The starting compound (**2**) required for the synthesis of **3** was prepared (Bahner et al., 1952) *via* the reaction of **1** with α-bromo ketones in the presence of K_2CO_3 in 1,4-dioxane at 70–75 °C for 3–4 h. Initially, in certain cases the compound **2** was isolated and purified before use in the next step. However, at a later stage we observed that the purification of compound **2** was not necessary and the crude product isolated after usual work up could be used for the preparation of the target compound **3**. Nevertheless, to establish the optimized reaction conditions we used the cyclization of 2-(3,4-dihydroquinolin-1(2*H*)-yl)-1-phenylethanone (**2a**) as a model reaction (Table 1). The reaction was performed in MeCN using various acid catalysts e.g. AcOH, CF_3CO_2H and *p*-TSA (*p*-toluenesulfonic acid) (entries 1–3, Table 3) when the desired product **3a** was isolated in low yield only in third case (entry 3, Table 1). The change of solvent to toluene did not improve the product yield significantly (entry 4, Table 1). However, **3a** was isolated in 53% yield when the reaction was performed in 1,4-dioxane (entry 5, Table 1). The duration of all these reactions was 24 h. To decrease the reaction time we performed the reaction under ultrasound irradiation using a laboratory ultrasonic bath SONOREX SUPER RK 510H model producing irradiation of 35 kHz. To our delight the reaction was completed within 2 h affording **3a** in 67% yield (entry 6, Table 1). All these reactions in the absence or presence of ultrasound were generally performed at 80 °C. The lowering of reaction temperature decreased the yield of **3a** considerably (entry 7, Table 1). Thus, the condition of entry 6 was found to be optimum and used for further study.

Table 1 The effect of reaction conditions on the conversion of **2a** to **3a**.[a]



Entry	Catalyst	Solvent	Time (h)	% Yield[b]
1	AcOH	MeCN	28	0
2	CF_3CO_2H	MeCN	28	Trace
3	*p*-TSA	MeCN	28	21
4	*p*-TSA	Toluene	28	27
5	*p*-TSA	1,4-Dioxane	28	53
6	*p*-TSA	1,4-Dioxane	2	67[c]
7	*p*-TSA	1,4-Dioxane	2	49[c,d]

[a] All the reactions were performed using **2a** (1 mmol) and catalyst (0.5 mmol) in a solvent (3 mL) at 80 °C under nitrogen.
[b] Isolated yield.
[c] The reaction was performed in the presence of ultrasound.
[d] The reaction was performed at 50 °C instead of 80 °C.

To extend the scope and generality of this methodology, a number of ethanone derivatives (**2**) were treated with *p*-TSA in 1,4-dioxane under the conditions of entry 6 of Table 1. Both aromatic and aliphatic substituents as "R" group were examined (Table 2). The reaction proceeded well in all these cases affording the corresponding 6-substituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinoline derivatives (**3**) in good to acceptable yields (Table 2). Aromatic "R" moiety containing various type of substituents such as mild or strong electron-donating groups such as F, Cl, Br, Me, OMe (entries 1–6, Table 2) and electron-withdrawing such as CN (entry 7, Table 2) was examined and well tolerated except the case of CN. The presence of aromatic groups such as 2-naphthyl or benzofuran-2-yl was also tolerated (entries 8 and 9, Table 2). The aliphatic "R" moiety such as $-CH_2CO_2Et$ and ethyl (entrys 10 and 11, Table 2) was generally found to be tolerated under the condition employed though the product yield was not particularly high in the first case possibly due to the cleavage of ester group leading to the corresponding acid thereby partial loss of the product **3j**.

A plausible mechanism (Shikhaliev et al., 2003) for the ultrasound mediated synthesis of 6-substituted 2,3-dihydro-

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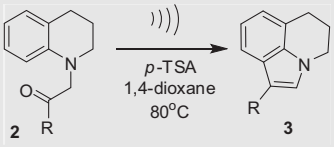
Table 2 Synthesis of 6-substituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinoline derivatives (**3**).[a]



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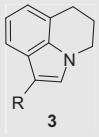
Entry	Substrate[b] **2**; R =	Product **3**	% Yield[c]
1	Ph	**3a**	67
2	C_6H_4F-*p*	**3b**	78
3	C_6H_4Cl-*p*	**3c**	76
4	C_6H_4Br-*p*	**3d**	73
5	C_6H_4Me-*p*	**3e**	83
6	C_6H_4OMe-*p*	**3f**	78
7	C_6H_4CN-*p*	**3g**	51
8	2-Naphthyl	**3h**	69
9	Benzofuran-2-yl	**3i**	70
10	CH_2CO_2Et	**3j**	60
11	Et	**3k**	82

[a] Reactions were performed using **2** (1 mmol) and *p*-TSA (0.5 mmol) in 1,4-dioxane (3 mL) at 80 °C under ultrasound for 2 h under nitrogen.
[b] The compound **2** prepared for this step was used without purifying further.
[c] Isolated yield.

Table 3 *In vitro* antiproliferative properties of compound **3** @ 10 μM against cancer and non-cancerous cells.



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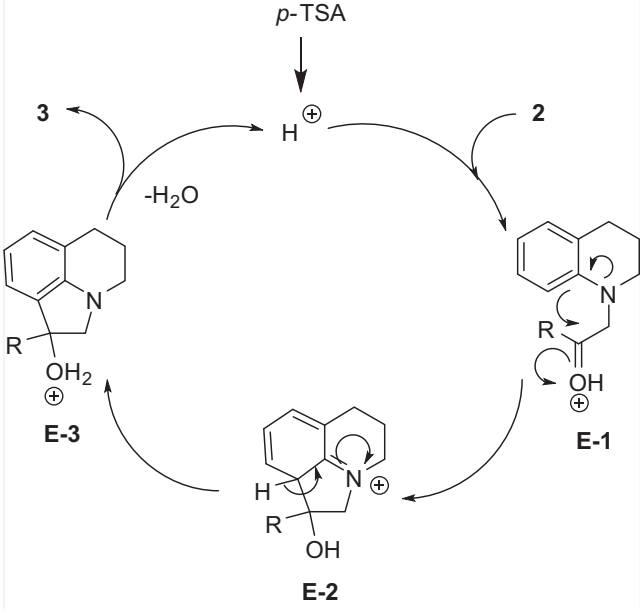
Entry	Compound **3**; R =	% Inhibition of proliferation[a]	
		K562 Leukemia	HEK293[b] Non-cancerous
1	**3a**; Ph	38.0	0.3
2	**3b**; C_6H_4F-*p*	50.9	0.5
3	**3c**; C_6H_4Cl-*p*	35.6	1.6
4	**3d**; C_6H_4Br-*p*	33.8	1.2
5	**3e**; C_6H_4Me-*p*	51.2	0.7
6	**3f**; C_6H_4OMe-*p*	65.7	2.8
7	**3g**; C_6H_4CN-*p*	33.8	2.1
8	**3h**; 2-Naphthyl	23.0	3.9
9	**3i**; Benzofuran-2-yl	24.8	2.4
10	**3j**; CH_2CO_2Et	35.1	1.6
11	**3k**; Et	21.1	0.8

[a] Data represent the mean values of three independent determinations.
[b] HEK293 cell line was used as noncancerous cell line.

1*H*-pyrrolo[3,2,1-*ij*]quinoline derivatives (**3**) in the presence of *p*-TSA is shown in Scheme 2. The cyclodehydration process seemed to proceed *via* generation of the protonated species **E-1** (from compound **2**) which on intramolecular cyclization afforded **E-2**. This intramolecular attack by the benzene ring was facilitated by the ring nitrogen of **E-1**. Re-aromatization of the benzene ring of **E-2** followed by protonation of the hydroxyl group afforded **E-3**. The elimination of water molecule from **E-3** and regeneration of proton completed the catalytic cycle affording the desired product **3**. It is worthy to note that electron donating or withdrawing effect of "R" group attached to the carbonyl moiety could influence the electropositivity of carbonyl carbon thereby intramolecular cyclization of **E-1**. Thus the *p*-cyanophenyl group due to its electron withdrawing effect did not allow adequate degree of polarization of $-C{=}OH^+$ bond to facilitate the intramolecular attack by the nucleophilic phenyl moiety at the carbonyl carbon.

The results of Table 1 (entry 5 vs. 6) clearly suggest that the synthesis of compound **3** was accelerated in the presence of ultrasound though it is not clear if the ultrasound irradiation has effect on one or more of steps shown in Scheme 2. It is possible that the force created due to the cavitational collapse can drive all the steps. Being a well known phenomenon cavitation caused by ultrasound is involved with the growth, oscillation, and collapse of bubbles under the action of an acoustic field (Mason and Peters, 1991; Mason, 2007). The cavitational collapse on the other hand creates drastic conditions inside the medium within an extremely short period of time. For example, the temperature of 2000–5000 K and pressure up to 1800 atmosphere can be produced inside the collapsing cavity under sonic conditions. Also, strong physical effects including shear forces, jets, and shock waves are caused by this collapse outside the bubble. Thus, chemical transformations performed under ultrasound proceed with notable efficiency and speed due to these cavitation-induced overall effects. This perhaps explains the rate acceleration of the present reaction under ultrasound in the absence of which the reaction took relatively longer time (entry 5, Table 1).



Scheme 2 Proposed reaction mechanism for the cyclodehydration of **2** leading to **3**.

Table 4 *In vitro* antiproliferative effects of compound **3f** against K562 Leukemia cells.

Compounds	% Inhibition of proliferation[a]				
	10 μM	5 μM	1 μM	0.1 μM	0.01 μM
3f	66	51	37	23	ND
Doxorubicin	82	70	59	47	32

ND = not determined.
[a] Average of three determinations.

3.2. Pharmacology

All the compounds of **3** synthesized based on the template **B** (Fig. 1) were evaluated for their potential anticancer properties *in vitro*. The cells used for our *in vitro* studies include human chronic myeloid leukemia cells such as K562, and non-cancerous human embryonic kidney cells such as HEK293. The effect of test compounds on cell viability was measured using a colorimetric MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-di phenyltetrazolium bromide] assay after 24 h of treatment in culture medium containing PBS. The percentages of cell viability for most promising test compounds at 10 μM are presented in Table 3. The compounds that showed > 50% activities were considered as active. As can be seen from Table 3 the compounds **3b**, **3e** and **3f** showed significant activities against K562 Leukemia cells whereas other compounds were found to be less active or inactive. It is evident that the *p*-substituent on the benzene ring of the ''R'' group played a key role and F, Me as well as OMe were found to be favorable. Notably, all these compounds were found to be selective toward the growth inhibition of cancer cells as none of these compounds showed any significant effects when tested against HEK293 cells. The best active compound **3f** was taken further for a dose response study (Table 4). The compound **3f** showed consistent dose-dependent growth inhibition of K562 Leukemia cells across all the concentrations tested. In view of the fact that leukemia affected 352,000 people globally and caused 265,000 deaths in 2012 (World Cancer Report, 2014), the compound **3f** was identified as a new cytotoxic agent and is of further interest.

4. Conclusion

In conclusion, a series of 6-substituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinoline derivatives were designed and synthesized as potential cytotoxic agents. Synthesis of these compounds was carried out by using a Bischler type reaction that involved the cyclodehydration of 2-(3,4-dihydroquinolin-1(2*H*)-yl)-1-alkyl/aryl ethanones in the presence of *p*-TSA under ultrasound irradiation. A number of compounds were prepared using this methodology and tested for their *in vitro* antiproliferative properties against cancer (leukemia) and non-cancerous cell lines. Some of the compounds showed promising and selective cytotoxic effects toward leukemia cells. Overall, our study suggests that the 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinoline framework could be an attractive template for the identification of novel and potential anticancer agents and the corresponding synthetic strategy described could be useful for generating diversity based library of small molecules related to this scaffold.

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